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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,749	12/22/2004	Takashi Nakayama	1422-0651PUS1	3018

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EXAMINER	
SGAGIAS, MAGDALINE K	
ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
12/10/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/518,749	NAKAYAMA ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/18/2009 has been entered.

Applicant's arguments filed 10/22/2009 have been fully considered but they are not persuasive. The amendment has been entered. Claims 1, 3-18 are pending and under consideration. Claims 2 and 19 have been canceled.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim **1, 3-4, 8-12, 13-18** rejected under 35 U.S.C. 103(a) as being unpatentable over **Tropepe et al** (Neuron, 30: 65–78, April, 2001); **Weiss et al**, (US 5,981,165) in view of **Suemori et al** (Developmental Dynamics, 222: 273–279, 2001).

Tropepe teaches a method for culturing in suspension mouse embryonic stem cells for a period of 7 days in the presence of LIF, or LIF plus FGF2 or LIF plus B27 conditioned medium to directly produce isolated neural cell (p 66 and figure 1) **(claim 1).** Tropepe teaches embryonic stem cells plated at limiting dilution in the presence of LIF, the frequency in which at least one neural stem cell will proliferate to form a sphere colony (see figure 1B) **(claim 4).** Tropepe teaches after 3 days in vitro or 7 days in vitro individual sphere colonies were transferred to a polyornithine substrate and allowed to adhere for 24 hr, in the presence of LIF and in the absence of EGF or FGF2 to obtain nestin positive neural cells (p 66, 2nd column, first paragraph and figure 1 and p 67 1st column figure 2) **(claims 8-11, 13).** Tropepe teaches individual colonies were placed on a matrigel substrate for period of 7 days and each of the differentiated colonies contained neurons positive for class III β tubulin (p 67, 2nd column, first paragraph) **(claim 14).** Tropepe teaches individual colonies were placed on a matrigel substrate for period of 7 days and each of the differentiated colonies contained neurons positive for the glial cell marker astrocytes (GFAP+) and oligodendrocytes (O4+) p 67, 2nd column, and figure 2A) **(claim 15).** Tropepe teaches the use of said ES cell model for mammalian neural development (p 75, 2nd column, 1st paragraph) **(claims 16-18). Weiss et al,** supplement the teachings of Tropepe by teachings a method for producing isolated mouse neural cells, by culturing a suspension of embryonic stem cells in the presence of ingredients equivalent to an astrocyte conditioned medium, (column 12, example 3) Further Weiss teaches the formation of neurospheres (figure 2). **Weiss** teaches a method of producing a neuron by carrying a suspension of embryonic stem cells in the presence of ingredients substantially equivalent to an astrocyte conditioned medium in the state of adhesion of the neural stem cells to an adhesive culture substratum by plating the cells onto poly-L-ornithine coated glass cover slips, in the complete medium with rat B49 glial cell line-derived conditioned medium in the

absence of bFGF, in the presence of FGF2 and in the presence of ingredients substantially equivalent to astrocyte conditioned medium (example 8). Weiss teaches the isolated neuron expresses tyrosine hydroxylase (example 2) (**claim 14**). Tropepe differs from the present invention for not teaching cynomolgus monkey embryonic stem cells for producing neural cells.

However, at the time the claimed invention was made, **Suemori et al** teach the derivation of ES cell lines from the rhesus monkey (*Macaca mulatta*) and common marmoset (*Callithrix jacchus*) with shared many characteristics with human ES cells (p 274, 1st column, 1st paragraph). **Suemori et al** teach because the cynomolgus monkey, as well as the rhesus monkey, belong to the Catarrhini, which are closely related to humans, and because they are widely used for medical research, cynomolgus monkey ES cells would be valuable for preclinical research before the clinical usage of human ES cells and such ES cells could be maintained for long periods as stem cells, and they showed differentiation in vitro and in vivo into various tissues indicating their pluripotency (p 274, 1st column, 1st paragraph). Sumeori teaches the cells were cryopreserved (p 274 2nd column bridges to p 275) **(claim 12).** Suemori suggest the cynomolgus ES cell lines established will provide a good model system for development of transplantation therapies using human ES cells (p 278, 2nd column).

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. ___, 82 USPQ2d 1385 (2007): "Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a

known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

Accordingly, it would have been obvious to the ordinarily skilled artisan to modify the teachings of Tropepe/Weiss to utilizing cynomolgus ES-cell derived neural cells, such as that taught by Suemori with a reasonable expectation of success. One of ordinary skill in art would have been motivated to make this modification in order to produce an unlimited source of donor cells (such as suggested by Suemori), see Abstract. One of skill in the art would readily recognize that an unlimited source of neural cells would also be useful to such ES cells could be maintained for long periods as stem cells, and they showed differentiation in vitro and in vivo into various tissues indicating their pluripotency as taught by Suemori.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims **5-7** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Tropepe et al** (Neuron, 30: 65–78, April, 2001); **Weiss et al,** (US 5,981,165) in view of **Vitkovíc et al.** (AIDS Res and Human Retroviruses, 7(9): 723-727, 1991) when taken with **Reubinoff et al**. (Nature Biotechnology, 19: 1134-1140, 2001 (IDS)) when taken with **Thomson et al**. (Science, 282: 1145-1147, 1998).

The teachings of Tropepe/ **Weiss** apply here as indicated above.

However, Tropepe/Weiss do not teach a method for producing neural cells in the presence of bFGF.

However, Vitkovíc teaches astrocyte-conditioned media from human astrocytes (p. 724, Cell Cultures and Media, 1st column). However, prior to the time of the claimed invention, Reubinoff teach the differentiation of human ES cells to produce astrocytes, as shown by the presence of GFAP (p. 1136, 2nd column, 4th paragraph). Reubinoff teaches in order to enhance the differentiation of the human ES cells towards the glial lineages, spheres were plated on poly-D--L-lysine and fibronectin in medium supplemented with bFGF (p 1139, 2nd column 3rd paragraph). **Thomson** et al teach that directing differentiation of ES cells to specific cell types will provide large, purified population of euploid human cells, which would provide a potentially limitless source of cells for drug discovery and transplantation therapies (see p. 1146-1147, bridging sentence).

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. ___, 82 USPQ2d 1385 (2007): "Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the

same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

Accordingly, it would have been obvious to the ordinarily skilled artisan to modify the teachings of Tropepe/Weiss/ to utilizing astrocyte derived medium as taught by Vitkovíc in combination with bFGF such as that taught by Reubinoff, with a reasonable expectation of success. One of ordinary skill in art would have been motivated to make this modification in order to produce an unlimited source of donor cells (such as suggested by Reubinoff), see Abstract. One of skill in the art would have been readily recognize that adding bFGF into the culture medium of Vitkovíc in order to enhance differentiation towards the glial lineage as taught by Reubinoff. In addition, one of skill in the art would readily recognize that an unlimited source of astrocytes would also be useful to produce astrocyte taken with the teachings of Thomson who teach that directing differentiation of ES cells to specific cell types will provide large, purified population of euploid human cells, which would provide a potentially limitless source of

cells for drug discovery and transplantation therapies (see p. 1146-1147, bridging sentence).

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 1, 3-18 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the amendment.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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/Anne-Marie Falk/
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